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Pyrrole and Oligopyrrole Synthesis by 1,3-Dipolar Cycloaddition of Azomethine Ylides with Sulfonyl Dipolarophiles

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Dedicated to Professor José Barluenga on the occasion of his 70th birthday

Abstract: A procedure for the synthesis of functionalized, substituted pyrroles by 1,3-dipolar cycloaddition of azomethine ylides has been developed. This protocol is based on the metal-catalyzed cycloaddition of α-iminoesters with sulfonyl dipolarophiles, followed by the base-promoted elimination of the sulfonyl groups. A wide variety of 2,5-disubstituted and 2,3,5- and 2,4,5-trisubstituted pyrroles have been prepared in satisfactory yields from 1,2-bis(sulfonyl ethylene), β-sulfonylenones, and β-sulfonylacrylates. This method can be applied in an iterative and straightforward manner to the construction of oligopyrroles, from bipyrroles to pentapyrroles. Iterative [*n*+1] and [*n*+2] approaches have been devised, the latter involves double 1,3-dipolar cycloaddition from pyrrolyl-based bis(iminoesters).

Keywords: cycloaddition · oligomerization · pyrroles · sulfones · ylides

Introduction

Pyrroles are among the most common heteroaromatic compounds and are present in a vast number of natural products[1] and biologically active compounds.[2] Furthermore, α,α-linked oligopyrroles are found in important families of natural products, such as prodigiosins[3] and porphyrins,[4] and have been the focus of much attention in materials science. For example, oligopyrroles have found applications in anion binding,[5] cation coordination,[6] conducting polymers,[7] liquid crystals,[8] and nonlinear optics.[9]

The interest of the pyrrole unit is exemplified by the great variety of procedures known for its synthesis,[10] which include the classical Knorr,[11] Paal–Knorr,[12] and Hantzsch syntheses.[13] The scope limitations of these classical methods, especially with regard to the preparation of functionalized substituted pyrroles, has prompted the development of novel methods for the synthesis of pyrroles. These include functionalization of simple pyrroles by metal-catalyzed coupling,[14] metal-catalyzed cyclization,[15] ring-contraction and -expansion procedures,[16] multicomponent reactions,[17] and [4+1][18] and [3+2] cycloadditions.[19] With regards to the last approach, very efficient procedures have been developed by cycloaddition of 1,3-azomethine ylides with activated alkynes then straightforward aromatization of the resultant dihydropyrrole.[20] In contrast, the related approach based on the cycloaddition of azomethine ylides with activated alkenes has been less explored due to the more difficult direct aromatization of pyrrolidines to pyrroles.[21] A practical solution to this limitation could rely on the use of activated alkenes, substituted with potential leaving groups, which would lead to pyrrolidines capable of ready transformation into the respective pyrroles by base-assisted elimination of the leaving groups. In this context, there are some successful examples of the synthesis of pyrroles that employ nitroalkenes[22] and activated haloalkenes as dipolarophiles,[23] but to the best of our knowledge this kind of approach has not been applied to the more challenging synthesis of bipyrroles and oligopyrroles. Keeping in mind the excellent ability of the sulfone unit to act both as an electron-withdrawing and a leaving group,[24] we envisaged that sulfonyl-substituted alkenes could play a dual role 1) as reactive dipolarophiles in the 1,3-dipolar cycloaddition with azomethine ylides derived from α-iminoesters (**1**); 2) by the provision of a leaving

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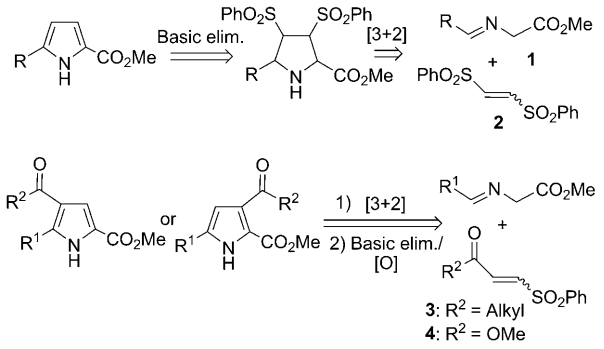
group to assist aromatization to the desired pyrrole product by basic elimination of the sulfonyl group.

In a previous communication,[25] we applied this strategy to the synthesis of 2,5-disubstituted pyrroles and α,α-linked oligopyrroles by using *trans*-1,2-bis(phenylsulfonylethylene) (**2**) as a dipolarophile and base-promoted elimination of both sulfonyl groups. Herein, we describe in detail the usefulness of this bis(sulfonyl) dipolarophile, as well as the readily available β-sulfonylenones (**3**) and β-sulfonylacrylates (**4**),[26] in the synthesis of substituted pyrroles, bipyrroles, and α,α-linked oligopyrroles (Scheme 1).



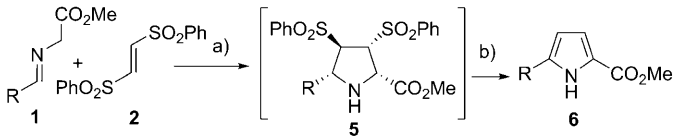
Scheme 1. Strategy for pyrrole synthesis.

Results and Discussion

Synthesis of pyrroles: Copper and silver Lewis acids are particularly appropriate catalysts in 1,3-dipolar cycloadditions with stabilized azomethine ylides derived from α-iminoesters.[27] We had previously described that $[Cu(CH_3CN)_4][PF_6]$ was a very effective catalyst in the asymmetric 1,3-dipolar cycloaddition of **2** with the azomethine ylides of α-iminoesters in the presence of chiral 2-(*tert*-butyl-sulfenyl)-1-(diphenylphosphino)ferrocene (FeSulPhos) ligands.[28] Thus, for the nonenantioselective version of this process we chose similar reaction conditions but by using PPh_3 as ligand: $[Cu(CH_3CN)_4][PF_6]$ (3 mol%), PPh_3 (3 mol%), and Et_3N (18 mol%). In the model reaction between *N*-benzylidene glycine methyl ester (**1a**) and **2**, complete conversion was observed after 5 h and a single bis(sulfonyl) adduct, **5a**, was isolated by standard silica-gel chromatography.[28] However, for conversion of **5a** to the pyrrole it is more convenient and efficient to include the direct addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to the crude reaction mixture to promote the easy in situ elimination of both sulfonyl groups. The expected pyrrole, **6a**, was isolated in 90% yield after final chromatographic purification (Table 1, entry 1). The stereoisomer of the dipolarophile, (*Z*)-**2**, was also tested under the same reaction conditions (Table 1, entry 2), but this alkene proved to be much less reactive than the *trans* isomer and provided the pyrrole **6a** in only 27% yield.

This procedure for the synthesis of 5-substituted pyrrole 2-carboxylic esters **6** by 1,3-dipolar cycloaddition with the bis(sulfone) **2** displays a great tolerance with regard to the substitution on the α-iminoester precursor. Aromatic (Table 1, entries 3 and 4), heteroaromatic (Table 1, entries 5 and 6), α,β-unsaturated (Table 1, entry 7), and aliphatic substituents (Table 1, entries 8 and 9) can be used. The corresponding pyrroles were afforded in good overall yields (72–97%).

Table 1. One-pot synthesis of 2,5-disubstituted pyrroles **6** from **2**.[a,b]



Entry	α-Iminoester	R	Pyrrole **6**	Yield [%][c]
1	**1a**	Ph	**6a**	90
2[d]	**1a**	Ph	**6a**	27
3	**1b**	4-$MeOC_6H_4$	**6b**	72
4	**1c**	3-FC_6H_4	**6c**	93
5	**1d**	2-furyl	**6d**	72
6	**1e**	2-thienyl	**6e**	97
7	**1f**	Ph–CH=CH	**6f**	88
8	**1g**	*t*Bu	**6g**	80
9	**1h**	Cy	**6h**	86

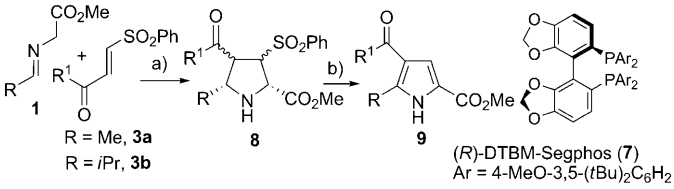
[a] Conditions (cycloaddition): $[Cu(CH_3CN)_4][PF_6]$ (3 mol%), PPh_3 (3 mol%), Et_3N (18 mol%), THF, RT, 5 h. [b] Conditions (basic elimination): DBU (2 equiv), THF, RT, 30 min. [c] Isolated yield after silica-gel chromatography. [d] (*Z*)-**2** was used as the dipolarophile.

With these results in hand, we turned to asymmetrically substituted sulfonyl dipolarophiles, the β-sulfonylenones **3**.[29] Unlike the bis(sulfone) **2**, dipolarophile **3** could give rise to regioisomeric mixtures of pyrroles. Copper-catalyzed 1,3-dipolar cycloaddition with the model ester **1a** under the previous conditions ($[Cu(CH_3CN)_4][PF_6]/PPh_3/Et_3N$) occurred very rapidly, albeit with a disappointing regioselectivity. This result was not very surprising because in our previous studies on the Cu-catalyzed asymmetric version of this reaction only Segphos-type ligands, such as **7**, provided a high regioselectivity in the cycloaddition.[26b] With these ligands, the C4-acetyl-substituted pyrrolidines **8** were selectively obtained as the major regioisomer (mainly as *exo* isomers), which showed that the regioselectivity is mainly controlled by the acetyl group of the dipolarophile rather than the sulfonyl group. Thus, we applied these reaction conditions ($[Cu(CH_3CN)_4][PF_6]$, DTBM-Segphos (**7**), Et_3N, Et_2O, RT) to the cycloaddition of **1a** with **3a**, followed by desulfonylation/aromatization by treatment of the crude pyrrolidine mixture with DBU. Under these conditions, pyrrole **9a** was isolated in 62% yield after chromatographic purification (Table 2, entry 1).

A good yield was also obtained in the reaction of **1a** with the bulkier isopropyl ketone dipolarophile **3b** (Table 2, entry 9).

Next, we studied the scope of this procedure with regard to the substitution at the iminoester. Acceptable to good yields were obtained with aryl- (Table 2, entries 2–5), heteroaryl- (Table 2, entries 6 and 7), and alkyl-substituted (Table 2, entry 8) azomethine ylides.

Table 2. Synthesis of 4-acyl-2,5-disubstituted pyrroles **9** from β-sulfonylenones **3**.[a,b]

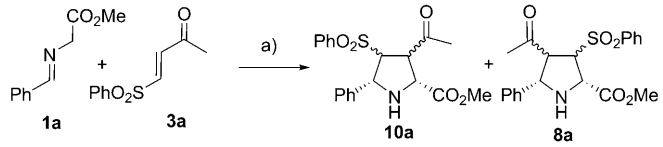


Entry	α-Iminoester	R	R^1	Pyrrole **9**	Yield [%][c]
1	**1a**	Ph	Me	**9a**	62
2	**1i**	2-naphthyl	Me	**9i**	52
3	**1j**	4-BrC_6H_4	Me	**9j**	63
4	**1k**	4-ClC_6H_4	Me	**9k**	68
5	**1l**	2-$MeOC_6H_4$	Me	**9l**	62
6	**1d**	2-furyl	Me	**9d**	68
7	**1e**	2-thienyl	Me	**9e**	60
8	**1h**	Cy	Me	**9h**	56
9	**1a**	Ph	*i*Pr	**9m**	79

[a] Conditions (cycloaddition): $[Cu(CH_3CN)_4][PF_6]$ (3 mol%), **7** (3.3 mol%), Et_3N (18 mol%), Et_2O, RT, 5 h. [b] Conditions (basic elimination): DBU (2 equiv), CH_2Cl_2, RT, 6–24 h. [c] Overall yield after silica-gel chromatography.

Silver catalysts, especially AgOAc, have been widely used in 1,3-dipolar cycloadditions of azomethine ylides. Interestingly, when this catalyst was tested in the model reaction of enone **3a** with the α-iminoester **1a** the regioselectivity was opposite to that observed in the Cu-catalyzed process; the 3-acetyl pyrrolidine **10a** is now the major regioisomer (**10a**/**8a** = 69:31, Table 3, entry 1). These results show that under

Table 3. Ag-catalyzed 1,3-dipolar cycloaddition of α-iminoester **1a** with β-sulfonylenone **3a**.[a]



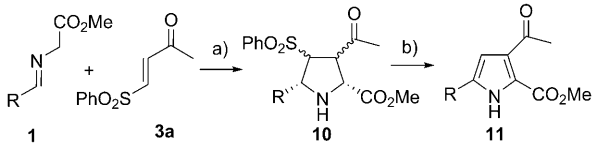
Entry	Ligand	Time [min]	**10a**/**8a**[b]
1	–	105	69:31
2	PPh_3	10	69:31
3	phenanthroline	10	71:29
4	TMEDA	10	75:25

[a] Conditions: AgOAc (10 mol%), ligand (10 mol%), Et_3N (20 mol%), THF, 5 h, RT. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture.

Ag-catalyzed reaction conditions the regioselectivity of the process is mainly controlled by the sulfonyl group rather than the ketone unit.[30] A significant increase in the reactivity and a similar regioselectivity were observed in the presence of ligands such as PPh_3, phenanthroline, or *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethane (TMEDA) (Table 3, entries 2–4). The optimal regioselectivity was obtained with AgOAc/TMEDA as the catalyst system (Table 3, entry 4, **10a**/**8a** = 75:25). Once isolated, this regioisomeric mixture was used directly in the desulfonylation/aromatization step.

Upon treatment with DBU, the regioisomer **10a**[31] was less prone than **8a** to suffer desulfonylation/aromatization to give the corresponding pyrrole. The best result was achieved in toluene at 70 °C, which led to pyrrole **11a** in 53% yield. A more efficient process was achieved by using 4-dimethylaminopyridine (DMAP) as a base to promote desulfonylation and consequent formation of the 2,5-dihydropyrrole intermediate. This intermediate was readily oxidized to pyrrole **11a** by addition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to the crude reaction mixture (64% overall yield from **3a**). As shown in Table 4, application of the

Table 4. Synthesis of 3-acyl-2,5-disubstituted pyrroles **11** from β-sulfonylenone **3a**.[a,b]



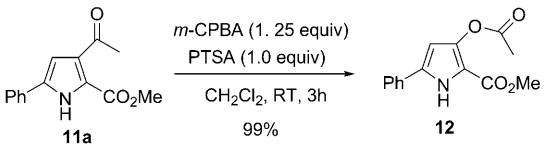
Entry	α-Iminoester	R	Pyrrole **11**	Yield [%][c]
1	**1a**	Ph	**11a**	64
2	**1k**	4-ClC_6H_4	**11k**	56
3	**1l**	2-$MeOC_6H_4$	**11l**	59
4	**1i**	2-naphthyl	**11i**	47
5	**1e**	2-thienyl	**11e**	40
6	**1h**	Cy	**11h**	49

[a] Conditions (cycloaddition): AgOAc (10 mol%), TMEDA (10 mol%), Et_3N (20 mol%), THF, RT, 5 h. [b] Conditions (basic elimination/oxidation): 1) DMAP (2 equiv), CH_2Cl_2, RT, 12 h; 2) DDQ (1.5 equiv), CH_2Cl_2, RT, 5 min. [c] Overall yield from **3a** after silica-gel chromatography.

Ag-catalyzed 1,3-dipolar cycloaddition and the two-step aromatization procedure gave acceptable overall yields (40–64%) for the formation of 3-acetyl pyrroles **11** from a variety of aryl-, heteroaryl-, and alkyl-substituted iminoesters **1**.

With the aim of applying the methodology described above to the preparation of pyrroles with electron-rich substituents,[32] we examined the conversion of 3-acetylpyrrole **11a** into 3-acetoxypyrrole **12** by Baeyer–Villiger oxidation. The reaction under standard conditions (*m*-chloroperbenzoic acid (*m*-CPBA), CH_2Cl_2, RT) was very slow and afforded the ester **12** in low yield after 24 h (22%). Gratifyingly, a much faster and cleaner reaction occurred in the presence of an acid, such as *p*-toluenesulfonic acid (PTSA) and the 3-acetoxypyrrole **12** was produced in nearly quantitative yield (Scheme 2).

With regard to the 1,3-dipolar cycloaddition of β-sulfonylacrylates, we had previously studied the catalytic asymmetric reaction of (*Z*)-**4** with α-iminoesters (Cu/Segphos as the catalyst system). We found that the reaction occurred with complete *exo* selectivity and that the regioselectivity was mainly controlled by the sulfonyl group.[26a] This regiochemical outcome is in agreement with the higher activation effect of the phenylsulfonyl group relative to the ester

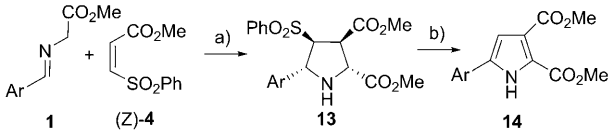


Scheme 2. Baeyer–Villiger oxidation of pyrrole **11a**.

moiety, evidenced in the Diels–Alder reactions of β-sulfonylacrylates.[33] In the reaction of (*Z*)-**4** with the model α-iminoester **1a** a high regioselectivity was also observed when $[Cu(CH_3CN)_4][PF_6]/PPh_3$ was used as the catalyst system, *exo*-**13a** was isolated as the major regioisomer in 81% yield.[34] Aromatization of **13a** to the equivalent pyrrole was achieved with the procedure previously developed for β-sulfonylenones; DMAP-mediated desulfonylation and in situ aromatization of the resulting dihydropyrrole by treatment with DDQ provided pyrrole **14a** in 58% yield after purification (47% overall yield from **4**).

As shown in Table 5 pyrroles **14**, with electronically varied aromatic and heteroaromatic substitution at C-5, were obtained with reasonable overall yields from the sulfonyl dipolarophile **4** (42–61%) (Table 5, entries 1–6), and included *N-tert*-butoxycarbonyl (*N*-Boc) protected-aniline derivative **14m** (Table 5, entry 4).

Table 5. Synthesis of pyrrole 2,3-dicarboxylate esters **14** from (*Z*)-**4**.[a,b]



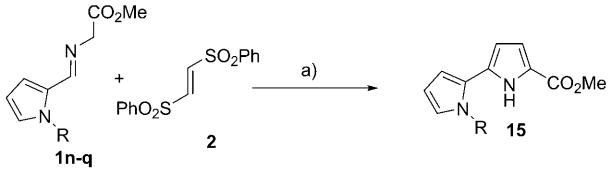
Entry	α-iminoester	Ar	Pyrrole **14**	Yield [%][c]
1	**1a**	Ph	**14a**	47
2	**1k**	4-ClC_6H_4	**14k**	61
3	**1l**	2-$MeOC_6H_4$	**14l**	51
4	**1m**	4-*N*-$(Boc)_2C_6H_4$	**14m**	51
5	**1i**	2-naphthyl	**14i**	42
6	**1d**	2-furyl	**14d**	57

[a] Conditions (cycloaddition): $[Cu(CH_3CN)_4][PF_6]$ (5 mol%), PPh_3 (5 mol%), Et_3N (18 mol%), CH_2Cl_2, RT, 5 h. [b] Conditions (basic elimination/oxidation): 1) DMAP (2 equiv), CH_2Cl_2, RT, 12 h; 2) DDQ (1.5 equiv), CH_2Cl_2, RT, 5 min. [c] Overall isolated yield from **4**. Both the pyrrolidine intermediate **13** (see the Supporting Information for isolated yields) and the pyrrole **14** were purified by silica gel chromatography.

Synthesis of bipyrroles: The preparation of α,α-linked bipyrroles deserves special consideration because they have served as precursors for the synthesis of prodigiosin[3a] and marineosin[3b] natural products, expanded porphyrins,[35] and for conductive oligopyrroles, polymers, and related structures.[7] Symmetrical bipyrroles can be efficiently prepared by oxidative coupling,[36] coupling of halopyrroles,[37] and desulfurization of thienodipyrroles.[38] In comparison, only a handful of methods have been reported for the synthesis of asymmetrically substituted bipyrroles and oligopyrroles,[39] mainly based on Vilsmeier condensations,[40] Paal–Knorr cyclizations,[41] couplings of pyrrolinones with pyrroles,[42] Ullmann couplings,[43] and other metal-catalyzed coupling processes.[44]

The procedure for the synthesis of pyrroles by 1,3-dipolar cycloaddition of azomethine ylides with sulfonyl dipolarophiles and further desulfonylation/aromatization could be straightforwardly applied to the synthesis of bipyrroles by using a pyrrolyl-substituted α-iminoester as azomethine ylide precursor. To verify this assumption, we first studied the cycloaddition/aromatization strategy with the bis-(sulfonyl) dipolarophile **2** (Table 6).

Table 6. One-pot synthesis of α,α-linked bipyrroles **15** from **2**.[a]



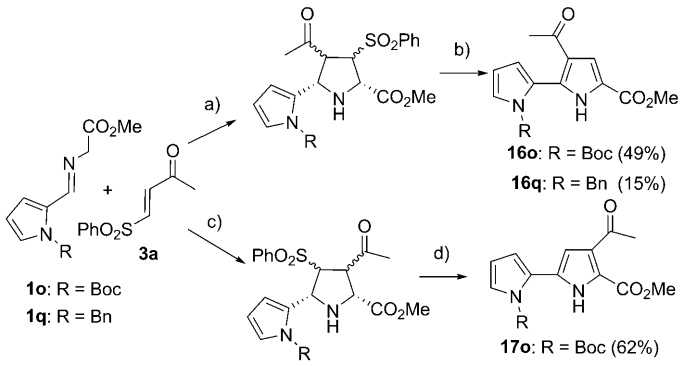
Entry	α-Iminoester	R	Bipyrrole **15**	Yield [%][b]
1	**1n**	H	–	–
2	**1o**	Boc	**15o**	67
3	**1p**	Ts	**15p**	61
4	**1q**	Bn	**15q**	78

[a] Conditions (cycloaddition): 1) $[Cu(CH_3CN)_4][PF_6]$ (3 mol%), PPh_3 (3 mol%), Et_3N (18 mol%), THF, RT, 5 h; 2) DBU (2 equiv), RT, 30 min. [b] Isolated yield after silica-gel chromatography.

Under the standard reaction conditions ($[Cu(CH_3CN)_4][PF_6]$, PPh_3, Et_3N, CH_2Cl_2; then DBU), a complex mixture of products was obtained from the N–H unprotected pyrrolylimino glycinate **1n** (Table 6, entry 1), which is likely to be due to competitive coordination of the pyrrole N–H unit with the copper catalyst. Gratifyingly, the protected *N*-Boc, *N*-tosyl (*N*-Ts), and *N*-benzyl (*N*-Bn) pyrrolylimino glycinates **1o**, **1p**, and **1q** (Table 6, entries 2–4) provided the expected bipyrroles **15o–q** in good overall yields. The best result (78%) was obtained with the *N*-Bn-protected iminopyrrole **1q**.

We extended this methodology to cycloadditions with the β-sulfonylenone dipolarophile **3a** (Scheme 3). In this case, the cycloaddition/aromatization strategy would provide easy access to trisubstituted bipyrroles with a 2,4,5- or 2,3,5-substitution pattern. This kind of substitution is present, for instance, in the bipyrrole core of prodigiosin and marineosin natural products.[3]

However, under the optimized conditions for the Cu-catalyzed process, the reaction from **1q** provided **16q** in very low yield (15%, Scheme 3). Interestingly, the *N*-Boc pyrrolyl analogue **1o** proved to be a suitable substrate and afforded the 4-acetyl bipyrrole **16o** in 49% overall yield. A similar reactive behavior was detected in the case of the Ag-catalyzed cycloaddition process (AgOAc/TMEDA); the *N*-Boc substrate **1o** was much more effective than the *N*-Bn analogue **1q**. In accordance with the usual regiochemical out-



Scheme 3. Synthesis of α,α-linked bipyrroles from β-sulfonylenone **3a**: a) $[Cu(CH_3CN)_4][PF_6]$ (3 mol%), **7** (3 mol%), Et_3N (18 mol%), Et_2O, RT, 5 h; b) DBU (2 equiv), CH_2Cl_2, RT, 30 min; c) AgOAc (10 mol%), TMEDA (10 mol%), Et_3N (20 mol%), THF, RT, 5 h; d) 1) DMAP (2 equiv), CH_2Cl_2, RT, 12 h; 2) DDQ (1.5 equiv), CH_2Cl_2, RT, 5 min.

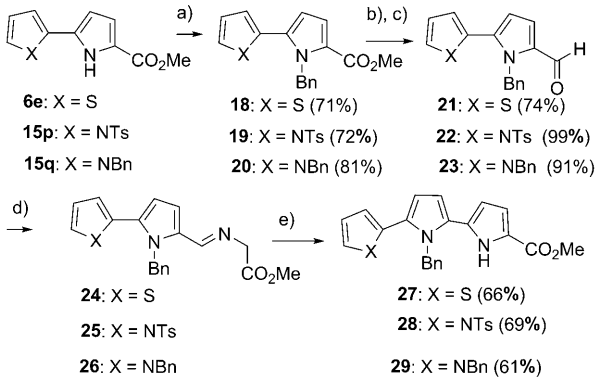
come of the Ag-catalyzed process, the cycloaddition/aromatization process from **1o** led selectively to the 3-acetyl bipyrrole **17o** (62% overall yield, Scheme 3).

Synthesis of oligopyrroles

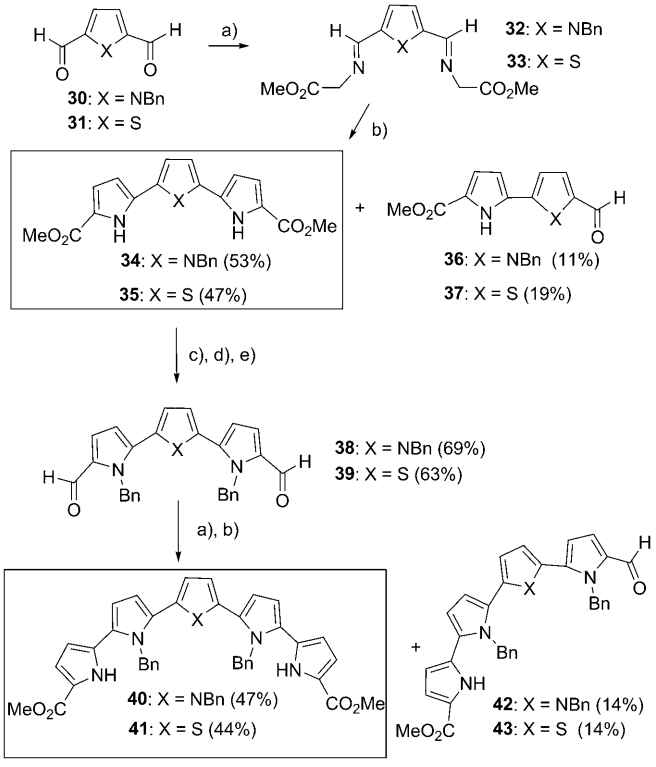
[n+1] strategy: Encouraged by the efficiency of this procedure for the synthesis of bipyrroles, we sought to examine the preparation of terpyrroles through iterative application of the pyrrole ring construction sequence. To test this approach, we chose thienylpyrrole **6e** and bipyrroles **15p** and **15q** as model substrates (Scheme 4). The benzylation of the free-NH group in bipyrroles **15p** and **15q** under usual conditions (BnBr, NaH, DMF) afforded the fully protected bipyrroles **19** and **20**. Subsequent conversion of the methyl ester moiety to the formyl derivative by application of a straightforward reduction ($LiAlH_4$)/oxidation (MnO_2) sequence provided the aldehydes **21**, **22**, and **23** in good yields. These aldehydes were then subjected to condensation with glycine methyl ester to afford the key bipyrrole α-iminoesters **24**, **25**, and **26**. Once isolated, these azomethine ylide precursors were immediately submitted to 1,3-dipolar cycloaddition with the bis(sulfone) **2** under the standard Cu-catalyzed reaction conditions. In situ DBU-promoted desulfonylation afforded the terpyrroles **28** and **29** and the related compound **27** in good overall yields (61–69% from the aldehydes **21**–**23**). Interestingly, this modular approach for the introduction of the pyrrole units allows the selective construction of orthogonally protected terpyrroles, such as **28**, as well as mixed heterocyclic systems, such as the thienylbipyrrole **27**. In addition, these terpyrroles could be used as building blocks in the preparation of highly valuable, substituted polypyrroles and expanded porphyrins.[35]

[n+2] strategy: To accelerate the process of construction of higher-order oligoheterocycles, we envisaged the possibility for the generation of two pyrrole rings in a single synthetic operation from a bis(α-iminoester) as double azomethine ylide precursor. This [1+2] and [1+2+2] approach from *N*-benzyl pyrrole 2,5-dicarbaldehyde (**30**) and thiophene 2,5-dicarbaldehyde (**31**) is shown in Scheme 5.

The formation of the bis(α-iminoester) precursor proved to be more of a challenge than expected. Under the usual conditions, the condensation of the pyrrole dialdehyde **30**[45]



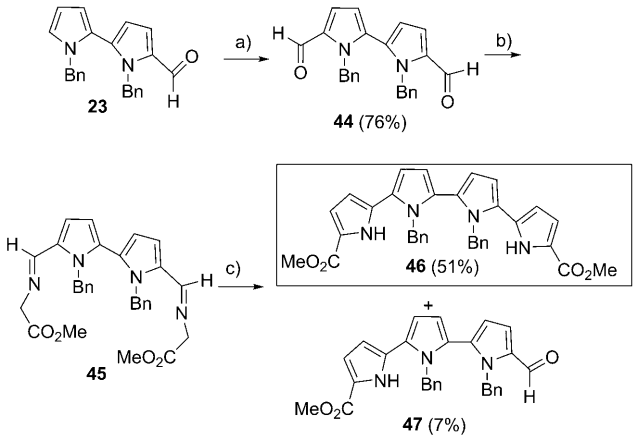
Scheme 4. Synthesis of the terpyrroles **28** and **29** and the thienylbipyrrole **27**: a) BnBr, NaH, DMF, RT, 12 h; b) $LiAlH_4$, THF, 0 °C, 3 h; c) MnO_2, acetone, RT, 14 h; d) glycine methyl ester hydrochloride (1.3 equiv), Et_3N, $MgSO_4$, RT, 15 h; e) **2** (1.5 equiv), $[Cu(CH_3CN)_4][PF_6]$ (3 mol%), PPh_3 (3 mol%), Et_3N (18 mol%), THF, RT, 5 h; then DBU (2 equiv), RT, 30 min.



Scheme 5. Synthesis of the pentaheterocycles **40** and **41**: a) glycine methyl ester hydrochloride (4 equiv), Et_3N, EtOH, SiO_2, RT, 2 h; b) **2** (4 equiv), $[Cu(CH_3CN)_4][PF_6]$ (3 mol%), PPh_3 (3 mol%), Et_3N (18 mol%), CH_2Cl_2, 4 Å molecular sieves, RT, 5 h; then DBU (4 equiv), RT, 30 min; c) BnBr, NaH, DMF, RT, 12 h; d) $LiAlH_4$, THF, 0 °C, 3 h; e) MnO_2, acetone, RT, 14 h.

with an excess of glycine methyl ester in the presence of the usual dehydrating agents, such as $MgSO_4$, $NaSO_4$, or molecular sieves, was accompanied by incomplete conversion or the formation of side products. Interestingly, the bis(α-iminoester) was cleanly formed in high yield when silica gel was used as a dehydrating agent under sonication in ethanol.[46] Once isolated, crude bis(imine) **32** was immediately treated with an excess of bis(sulfone) **2** under the usual Cu-catalyzed reaction conditions, but in the presence of molecular sieves to minimize the imine hydrolysis side-reaction. In situ DBU-mediated desulfonylation then chromatographic purification afforded the expected symmetrical terpyrrole **34** as the main product (53% yield from dialdehyde **30**), along with a minor amount of the bipyrrole aldehyde **36** (11% yield)—the result of a monocycloaddition process and hydrolysis of the second imine unit.[47] The conversion of the terpyrrole diester **34** into the N-protected terpyrrole dialdehyde **38**, required for the further preparation of the pentapyrrole derivative, was efficiently performed in three steps, as previously developed in the iterative [*n*+1] strategy (N-benzylation, ester reduction, MnO_2 oxidation of the alcohol). The dialdehyde **38** was then submitted to double pyrrole ring construction, by 1,3-dipolar cycloaddition of its bis(α-iminoester) with bis(sulfone) **2**, to provide pentapyrrole **40** as the main product (47% overall yield). In this reaction, the quaterpyrrole aldehyde **42** (from the competitive monocycloaddition process) was also isolated as a minor product (14% yield). Additionally, the application of this [1+2+2] strategy to thiophene dialdehyde **31** provided the triheterocycle **35** (47% yield) and subsequently the pentaheterocycle **41** (44% yield from dialdehyde **39**), which illustrates the generality of this iterative method for the synthesis of α,α-linked oligoheterocycles.

To complement the previous syntheses of odd-numbered oligopyrroles, we applied a similar strategy to the synthesis of even-numbered oligopyrroles, such as quaterpyrroles, by means of a [2+2] construction approach (Scheme 6). Vilsmeier formylation[48] of the previously prepared bipyrrole aldehyde **23** provided the symmetrical bipyrrole dialdehyde **44** (76% yield), suitable for the two-directional sequence. The formation of bis(α-iminoester) **45**, followed by 1,3-dipolar cycloaddition of **45** with **2** and DBU-promoted desulfonylation, afforded the quaterpyrrole **46** in 51% yield. A minor amount (7%) of the terpyrrole **47**, a result of the monocycloaddition process, was also isolated.



Scheme 6. Synthesis of the quaterpyrrole **46**: a) $POCl_3$, DMF, 0°C to RT, 12 h; b) glycine methyl ester hydrochloride (4 equiv), Et_3N (4 equiv), EtOH, SiO_2, RT, 2 h; c) **2** (3 equiv), $[Cu(CH_3CN)_4][PF_6]$ (3 mol%), PPh_3 (3 mol%), Et_3N (18 mol%), CH_2Cl_2, 4 Å molecular sieves, RT, 5 h; then DBU (4 equiv), RT, 30 min.

Conclusion

We have described a novel process for the preparation of substituted pyrroles based on the metal-catalyzed 1,3-dipolar cycloaddition of α-iminoesters with readily available sulfonyl dipolarophiles, such as bis(sulfonylethene), β-sulfonyl acrylates, and β-sulfonylenones, followed by base-promoted sulfone elimination and aromatization. This methodology provides access to 2,5-disubstituted and 2,3,5- and 2,4,5-trisubstituted pyrroles. Furthermore, this pyrrole construction protocol can be iteratively applied to the preparation of α,α-linked bipyrroles, oligopyrroles, and related oligoheterocycles by conversion of the ester moiety of the pyrrole unit into an α-iminoester functionality. Both [*n*+1] and [*n*+2] strategies, in which the latter case involves a double cycloaddition process, have been developed and allow the preparation of bipyrroles, terpyrroles, quaterpyrroles, and pentapyrroles.

Experimental Section

Typical procedure for the synthesis of 2,5-disubstituted pyrroles (6a): A solution of **1a** (60 mg, 0.34 mmol) in dry THF (1 mL) and Et_3N (13 μL, 0.09 mmol) was successively added to a solution of PPh_3 (2.8 mg, 0.01 mmol) and $[Cu(CH_3CN)_4][PF_6]$ (3.8 mg, 0.01 mmol) in dry THF (1 mL) under nitrogen atmosphere at RT. The resulting solution was added to a suspension of **2** (193 mg, 0.51 mmol) in dry THF (1 mL). The mixture was then stirred for 5 h before DBU (93 μL, 0.68 mmol) was added. After 30 min, the mixture was filtered through a plug of Celite with the aid of CH_2Cl_2 (5 mL) and the solvent was removed under reduced pressure. The residue was purified by silica-gel flash chromatography (hexane/EtOAc 5:1) to afford the pyrrole **6a**[49] (148 mg, 90%, yellow solid). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.58$ (brs, 1H), 7.46 (d, $J = 7.6$ Hz, 2H), 7.28–7.23 (m, 2H), 7.18–7.11 (m, 1H), 6.84–6.82 (m, 1H), 6.42–6.39 (m, 1H), 3.73 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.9$, 137.2, 131.1, 128.9, 127,6, 124.8, 122.8, 116.9, 107.9, 51.6 ppm.

Typical procedure for the synthesis of 2,4,5-trisubstituted pyrroles (9a): A solution of **1a** (61 mg, 0.34 mmol) in Et_2O (1 mL) and Et_3N (8 μL, 0.057 mmol) were successively added to a solution of **7** (11.1 mg, 9.4×10^{-3} mmol) and $[Cu(CH_3CN)_4][PF_6]$ (3.2 mg, $8.5\ 10^{-3}$ mmol) in Et_2O (1 mL) under nitrogen atmosphere at RT. The resulting solution was added to a suspension of **3a** (60 mg, 0.28 mmol) in Et_2O (1 mL). The mixture was stirred for 10 min, filtered through a plug of Celite with the aid of CH_2Cl_2 (5 mL), and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL) and DBU (120 μL, 0.86 mmol) was added. After stirring for 6 h, CH_2Cl_2 (10 mL) and saturated aqueous solution of NH_4Cl (10 mL) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2× 5 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 3:1) to afford **9a** (43 mg, 62%, white solid).

M.p. 130.0–132.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.43 (brs, 1H), 7.60–7.57 (m, 2H), 7.45–7.43 (m, 3H), 7.35 (d, J = 2.6 Hz, 1H), 3.85 (s, 3H), 2.37 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.7, 161.2, 139.8, 131.0, 129.4, 129.1, 128.4, 123.1, 121.9, 117.9, 51.9, 28.9 ppm; MS (FAB$^+$): m/z (%): 244.0 $[M+H]^+$ (80); HRMS (FAB$^+$): m/z: calcd for $C_{14}H_{14}NO_3$: 244.0974; found: 244.0978.

Typical procedure for the synthesis of 2,3,5-trisubstituted pyrroles (11a): A solution of **1a** (60 mg, 0.34 mmol) in THF (1 mL) and Et_3N (8 μL, 0.06 mmol) were successively added to a solution of TMEDA (4 μL, 0.03 mmol) and AgOAc (5.0 mg, 0.03 mmol) in THF (1 mL) under a nitrogen atmosphere at RT. The resulting solution was added to a suspension of **3a** (60 mg, 0.28 mmol) in THF (1 mL). The mixture was stirred for 15 h, filtered through a plug of Celite with the aid of CH_2Cl_2 (5 mL), and the solvent was removed under reduced pressure. The crude material was filtered through a short pad of SiO_2 (hexane/EtOAc 3:1) and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 mL) and DMAP (93 mg, 0.77 mmol) was added. After stirring for 12 h, CH_2Cl_2 (10 mL) and saturated aqueous solution of NH_4Cl (10 mL) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and DDQ (87 mg, 0.38 mmol) was added. After stirring for 5 min at RT, CH_2Cl_2 (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL) were added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 3:1) to afford **11a** (44 mg, 64%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.56 (brs, 1H), 7.58–7.54 (m, 2H), 7.45–7.40 (m, 2H), 7.37–7.31 (m, 1H), 6.87 (d, J = 3.2 Hz, 1H), 3.92 (s, 3H), 2.65 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7, 160.4, 135.0, 131.4, 130.2, 129.1, 128.4, 124.9, 121.0, 109.9, 52.1, 30.7 ppm; MS (FAB$^+$): m/z (%): 244.1 $[M+H]^+$ (40); HRMS (FAB$^+$): m/z: calcd for $C_{14}H_{14}NO_3$: 244.0974; found: 244.0971.

Typical procedure for the synthesis of pyrrole 2,3-dicarboxylate esters (14a): A solution of **1a** (468 mg, 2.6 mmol) in CH_2Cl_2 (5 mL), Et_3N (83 μL, 0.59 mmol), and a solution of **4** (500 mg, 2.2 mmol) in CH_2Cl_2 (5 mL) were sequentially added to a solution of PPh_3 (29 mg, 0.11 mmol) and $[Cu(CH_3CN)_4][PF_6]$ (41 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) under a nitrogen atmosphere at RT. The mixture was stirred for 5 h, filtered through a plug of Celite with the aid of CH_2Cl_2 (10 mL), and the solvent was removed under reduced pressure. The residue was purified by silica-gel flash chromatography (hexane/EtOAc 2:1) to afford the pyrrolidine **13a** (569 mg, 81%, white solid). M.p.156–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.80 (m, 2H), 7.64–7.60 (m, 1H), 7.52–7.47 (m, 2H), 7.19–7.15 (m, 3H), 7.09–7.06 (m, 2H), 5.00 (d, J = 3.4 Hz, 1H), 4.61 (d, J = 9.0 Hz, 1H), 3.91 (dd, J = 7.4, 3.4 Hz, 1H), 3.77 (s, 3H), 3.68 (dd, J = 9.0, 7.4 Hz, 1H), 3.58 (s, 3H), 2.74 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 168.8, 141.2, 138.4, 134.0, 129.2, 128.5, 128.4, 127.6, 126.1, 72.9, 62.1, 60.7, 52.5, 52.4, 47.1 ppm; HRMS (FAB$^+$): m/z: calcd for $C_{20}H_{22}NO_6S$: 404.1158 $[M]^+$; found: 404.1134.

DMAP (480 mg, 3.33 mmol) was added to a solution of **13a** (150 mg, 0.37 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred for 12 h at RT and CH_2Cl_2 (10 mL) and saturated aqueous solution of NH_4Cl (10 mL) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (4 mL) under nitrogen atmosphere at RT and DDQ (126 mg, 0.55 mmol) was added. After 5 min, the mixture was filtered through a plug of Celite with the aid of CH_2Cl_2 (5 mL) and the solvent was removed under reduced pressure. The residue was purified by silica-gel flash chromatography (hexane/EtOAc 3:1) to afford the pyrrole **14a** (56 mg, 58%, white solid). M.p. 133–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.69 (brs, 1H), 7.58–7.56 (m, 2H), 7.45–7.40 (m, 2H), 7.36–7.32 (m, 1H), 6.93 (s, 1H), 3.93 (s, 3H), 3.89 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3, 160.6, 134.8, 130.3, 129.1, 128.4, 124.8, 122.7, 121.5, 110.7, 52.2, 51.9 ppm; HRMS (FAB$^+$): m/z: calcd for $C_{14}H_{14}NO_4$: 260.0923 $[M+H]^+$; found: 260.0922.

Typical procedure for the synthesis of bipyrroles (15q): Compound **1q** (143 mg, 0.56 mmol) in dry THF (2 mL) and Et_3N (14 μL, 0.10 mmol) were successively added to a solution of PPh_3 (4.0 mg, 0.017 mmol) and $[Cu(CH_3CN)_4][PF_6]$ (6.0 mg, 0.016 mmol) in dry THF (2 mL) under a nitrogen atmosphere at RT. The resulting solution was added to a suspension of **2** (260 mg, 0.84 mmol) in dry THF (2 mL). The resulting mixture was stirred for 5 h before DBU (0.18 mL, 1.12 mmol) was added. After 30 min, the mixture was filtered through a plug of Celite with the aid of CH_2Cl_2 (5 mL) and the solvent was removed under reduced pressure. The residue was purified by silica-gel flash chromatography (hexane/EtOAc 5:1) to afford the bipyrrole **15q** (122 mg, 78%, white solid). M.p. 116–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.30 (brs, 1H), 7.30–7.22 (m, 3H), 6.99–6.96 (m, 2H), 6.82 (dd, J = 3.8, 2.5 Hz, 1H), 6.72 (dd, J = 2.7, 1.8 Hz, 1H), 6.40 (dd, J = 3.8, 2.5 Hz, 1H), 6.22 (dd, J = 3.7, 2.7 Hz, 1H), 6.02 (dd, J = 3.8, 2.6 Hz, 1H), 5.18 (s, 2H), 3.78 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 138.2, 129.1, 128.8, 127.5, 126.1, 125.4, 123.8, 122.0, 116.2, 109.3, 108.9, 108.6, 51.4, 50.9 ppm; MS (EI$^+$): m/z (%): 280 (100) $[M]^+$, 248 (33), 219 (23), 189 (81), 171 (28),157 (54), 129 (25), 102 (15), 91 (61), 65 (18); HRMS (EI$^+$): m/z: calcd for $C_{17}H_{16}N_2O_2$: 280.1211 $[M]^+$; found: 280.1210.

Typical procedure for the [*n*+1] strategy--conversion of bipyrrole 19 into terpyrrole 28: $LiAlH_4$ (2.0 M in THF, 63 μL, 0.12 mmol) was added dropwise to a solution of **19** (18 mg, 0.04 mmol) in dry THF (2 mL) at 0 °C. After 10 min at 0 °C, MeOH (3 mL) and a 1:1 saturated aqueous solution of sodium tartrate/EtOAc (10 mL) were added. The organic phase was separated, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to afford the bipyrrole alcohol as a yellow oil, which was used without further purification in the next step. MnO_2 (73 mg, 0.84 mmol) was added to a solution of the crude bipyrrole alcohol (17 mg, 0.04 mmol) in acetone (3 mL) at RT and the suspension was stirred for 12 h. The mixture was filtered through a plug of Celite with the aid of acetone and evaporated under reduced pressure. The residue was purified by silica-gel flash chromatography (hexane/EtOAc 6:1) to afford aldehyde **22** (17 mg, 99% from **19**, red oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.57 (s, 1H), 7.52–7.51 (m, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.22–7.17 (m, 5H), 6.98 (d, J = 3.9 Hz, 1H), 6.78–6.76 (m, 2H), 6.23 (t, J = 3.3 Hz, 1H), 6.16 (d, J = 3.9 Hz, 1H), 6.03–6.02 (m, 1H), 5.04 (s, 2H), 2.42 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.5, 145.4, 138.2, 135.2, 132.2, 132.1, 129.6, 128.3, 127.4, 127.0, 126.0, 124.5, 122.9, 122.6, 119.3, 115.2, 111.5, 49.2, 21.7 ppm; MS (FAB$^+$): m/z: 405.1 $[M+H]^+$; HRMS (FAB$^+$): m/z: calcd for $C_{23}H_{21}N_2O_3S$: 405.1273 $[M+H]^+$; found: 405.1276.

Et_3N (28 μL, 0.2 mmol) was added to a suspension of methyl glycinate hydrochloride (25 mg, 0.20 mmol) and microwave-activated 4 Å molecular sieves (385 mg) in dry toluene (5 mL). The mixture was stirred at RT for 30 min before **22** (52 mg, 0.13 mmol) was added. After 12 h at RT the mixture was filtered off and water (10 mL) was added. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to afford **25**, which was used in the next step without further purification (55 mg, 89%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (s, 1H), 7.48 (dd, J = 3.4, 1.7 Hz, 1H), 7.39–7.15 (m, 7H), 6.78–6.73 (m, 2H), 6.66 (d, J = 3.9 Hz, 1H), 6.19–6.14 (m, 1H); 6.05 (d, J = 3.9 Hz, 1H), 5.95 (dd, J = 3.4, 1.7 Hz, 1H), 5.04 (brs, 2H), 4.18 (s, 2H), 3.67 (s, 3H), 2.41 ppm (s, 3H).

A solution of α-iminoester **25** (55 mg, 0.12 mmol) in dry THF (0.5 mL) and Et_3N (5 μL, 0.035 mmol) were successively added to a solution of PPh_3 (1.0 mg, 0.0038 mmol) and $[Cu(CH_3CN)_4][PF_6]$ (1.4 mg, 0.0037 mmol) in dry THF (0.5 mL) under a nitrogen atmosphere at RT. The resulting solution was added to a suspension of **2** (57 mg, 0.18 mmol) in dry THF (0.5 mL). The resulting mixture was stirred for 5 h and DBU (55 μL, 0.37 mmol) was added. After 30 min, the mixture was filtered through a plug of Celite with the aid of CH_2Cl_2 (5 mL) and the solvent was removed under reduced pressure. The residue was purified by silica-gel flash chromatography (hexane/EtOAc 5:1) to afford the terpyrrole **28** (41 mg, 69%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (brs,

1H), 7.46 (dd, $J=3.3$, 1.8 Hz, 1H), 7.40 (d, $J=8.3$ Hz, 2H), 7.23–7.17 (m, 5H), 6.78–675 (m, 2H), 6.38 (d, $J=3.7$ Hz, 1H); 6.18–6–16 (m, 2H), 6.04–6.00 (m, 3H); 4.80 (s, 2H), 3.82 (s, 3H), 2.37 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=161.0$, 145.5, 138.7, 136.9, 135.2, 133.3, 129.6, 129.4 128.7, 127.6, 127.2, 125.5, 124.2, 123.8, 122.0, 118.7, 116.9, 113.5, 111.3, 109.2, 108.3 51.4, 48.7, 21.6 ppm; MS (FAB$^+$): m/z: 499.1 $[M]^+$; HRMS (FAB$^+$): m/z: calcd for $C_{28}H_{25}N_3O_4S$: 499.1565 $[M]^+$; found: 499.1572.

Typical procedure for the [*n*+2] strategy--conversion of terpyrrole dialdehyde 38 into pentapyrrole 40: A suspension of methyl glycinate hydrochloride (27 mg, 0.22 mmol) and Et_3N (30.6 μL, 0.22 mmol) in EtOH (1 mL) was stirred for 30 min at RT. The resulting solution was added to a mixture of **38** (28 mg, 0.054 mmol) and silica (43 mg) in EtOH (0.5 mL) and sonicated at RT for 2 h. The mixture was diluted with CH_2Cl_2 (5 mL) and filtered. The resulting solution was washed with water (5 mL), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to afford the crude bis(α-iminoester) (35.5 mg, 98%, yellow oil), which was immediately used in the next step without further purification. ^{1}H NMR (300 MHz, [D_6]benzene): $\delta=7.65$ (t, $J=1.1$ Hz, 2H), 7.07–6.92 (m, 13H), 6.60 (m, 2H), 6.43 (d, $J=3.96$ Hz, 2H), 6.20 (d, $J=3.96$ Hz, 2H), 6.18 (s, 2H), 5.65 (s, 4H), 4.44 (s, 2H), 3.87 (s, 4H), 3.27 ppm (s, 6H).

A solution of the freshly prepared bis(α-iminoester) (27 mg, 0.042 mmol) in dry CH_2Cl_2 (0.5 mL) and Et_3N (2 μL, 0.015 mmol) were successively added to a solution of PPh_3 (0.6 mg, 0.002 mmol), $[Cu(CH_3CN)_4][PF_6]$ (0.9 mg, 0.002 mmol) and microwave-activated 4 Å molecular sieves (480 mg) in dry CH_2Cl_2 (0.5 mL) under a nitrogen atmosphere at RT. The resulting solution was added to a suspension of **2** (38 mg, 0.125 mmol) in dry CH_2Cl_2 (0.5 mL). The resulting mixture was stirred for 5 h before DBU (25.1 μL, 0.17 mmol) was added. After 30 min, the mixture was filtered through a plug of Celite with the aid of CH_2Cl_2 (5.0 mL) and the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (hexane/EtOAc 6:1) to afford a mixture of the pentapyrrole **40** (14 mg, 47%, yellow solid) and the corresponding quaterpyrrole aldehyde **42** (3.6 mg, 12%, yellow solid). The products were kept at −20°C, under nitrogen atmosphere, and protected from the light. M.p. 80–82°C (decomposed); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.74$ (brs, 2H), 7.31–7.21 (m, 6H), 7.17–7.15 (m, 3H), 6.85–6.81 (m, 4H), 6.79 (dd, $J=3.8$, 2.6 Hz, 2H), 6.68–6.65 (m, 2H), 6.38 (d, $J=3.8$ Hz, 2H), 6.17 (d, $J=3.8$ Hz, 2H), 6.03 (s, 2H), 6.00 (dd, $J=3.8$, 2.6 Hz, 2H), 4.86 (s, 4H), 4.67 (s, 2H), 3.80 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=161.2$, 139.2, 139.1, 129.1, 128.8, 128.2, 127.3, 127.2, 126.9, 126.4, 126.2, 125.7, 125.5, 122.1, 116.1, 111.7, 111.1, 109.1, 108.9, 51.4, 48.3, 48.1 ppm; MS (FAB$^+$): m/z: 713.1 $[M]^+$; HRMS (FAB$^+$): m/z: calcd for $C_{45}H_{39}N_5O_4$: 713.1997 $[M]^+$; found: 713.3002.

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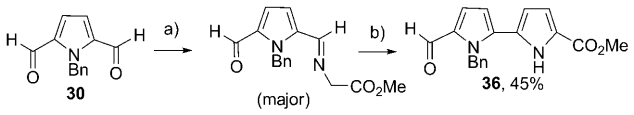

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